Role of VKA
in the expanding horizon of NOACs

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INTRODUCTION

- Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia, associated with a 4- to 5-fold increase in the risk of ischemic stroke
- Vitamin K antagonists (VKA; coumarins, like warfarin and acenocoumarol) have been the only oral anticoagulants available over the last 60 years
- These agents are undoubtedly effective to prevent stroke in patients with AF, but their management remains problematic due to their narrow therapeutic index and variability in drug exposure, necessitating routine coagulation monitoring (international normalised ratio (INR), food and drug interactions.

Conclusions from ARISTOTLE,ROCKET-AF & RE-LY

Class Effects:

- All three novel anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolization.
- All three agents reduce the risk of bleeding (fatal for Rivaroxaban, major for Apixaban, major at 110 mg for Dabigatran) and intracranial hemorrhage.
- The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year

Differentiators:

- Dabigatran at a dose of 150 mg was associated with a reduction in ischemic stroke
- Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding
- Apixaban was associated with a reduction in all cause but not CV mortality

Thrombosis
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Review Article

Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups

Antonio Gómez-Outes,[1] Ana Isabel Terleira-Fernández,[2,3] Gonzalo Calvo-Rojas,[4] M. Luisa Suárez-Gea,[1] and Emilio Vargas-Castrillón[2,3]

1561 articles, 27 of which related to clinical trials or protocols with rivaroxaban, dabigatran, or apixaban in AF. RE-LY study, ROCKET-AF and ARISTOTLE study were included. Also included 11 subanalyses of these trials that were considered relevant for the meta-analysis and 1 article corresponding to update of events reported in the RE-LY study. Five public reports from the US Food and Drug Administration website that included supplementary data of the RE-LY, ROCKET-AF, and ARISTOTLE studies, as well as one additional analysis of posttreatment events in the ROCKET-AF study and one additional subanalysis of the ARISTOTLE study were also included.

Few important conclusions…

- The NOAC were not more effective than warfarin in preventing nonhemorrhagic stroke and SEE in the overall study populations (RR = 0.93; CI 0.83 to 1.04).
- However, subgroup analyses suggest a **trend** towards superiority of the NOAC in centres with **TTR <65%.**
- Approximately 92% of the events were nonhemorrhagic strokes and only 8% were SEE.
- The separate results for nonhemorrhagic stroke (RR = 0.95; CI 0.85 to 1.07) and SEE (RR = 0.73; CI 0.50 to 1.07) were consistent with those of the composite endpoint.

Comparison of Trial Metrics

	RE-LY	ROCKET AF	ARISTOTLE
Time in Therapeutic Range (TTR)	64% **67% warfarin-experienced** 61% warfarin-naïve	Mean 55% Median 58%	Mean 62% Median 66%

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

- (FDA) Advisory Committee meeting reported that when warfarin was administered skillfully within the ROCKET-AF trial, and the TTR was above approximately 68%, there was a relative increase in primary outcome events in the rivaroxaban group

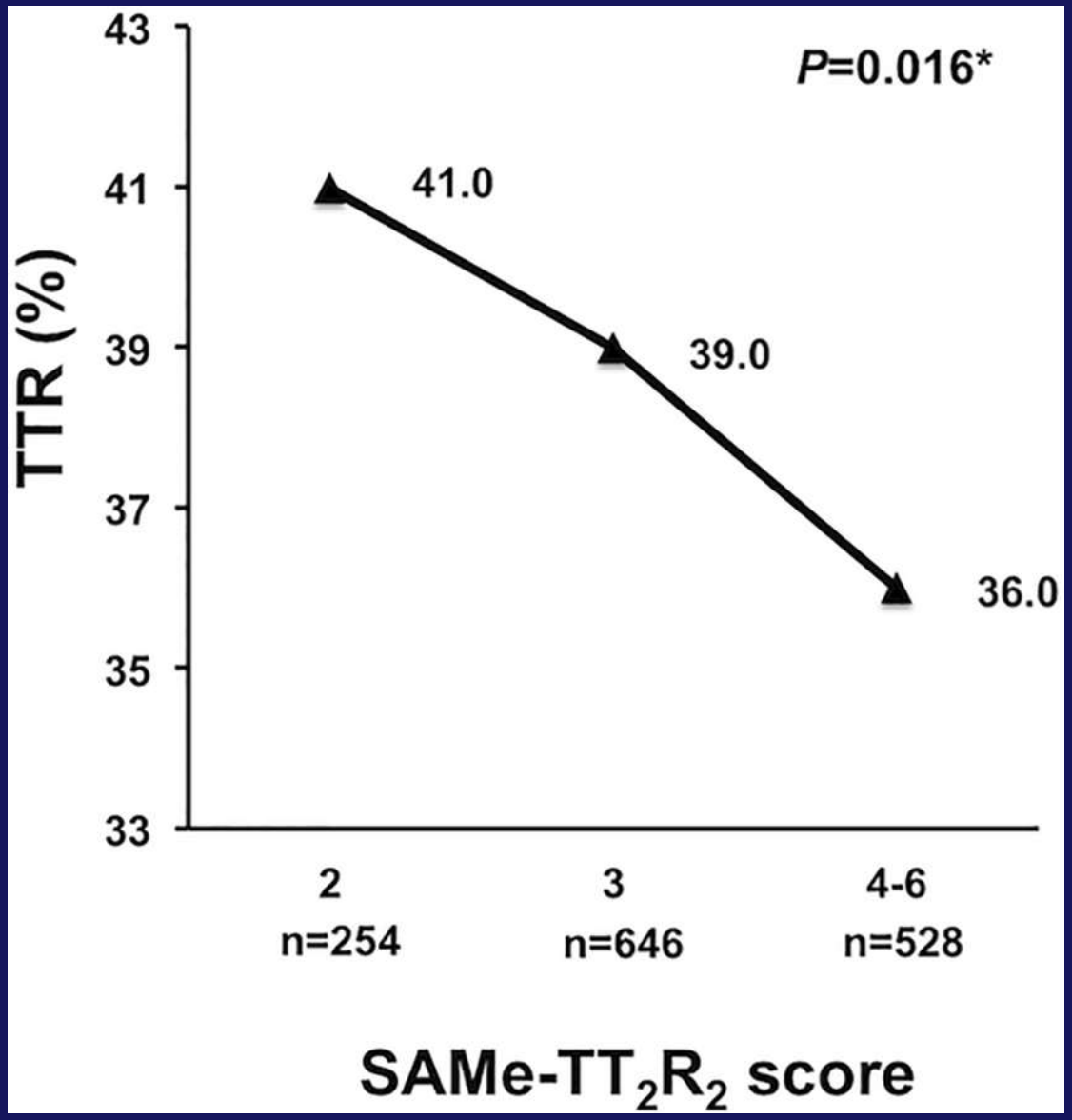
How to predict good TTR?

SAMe- TT2R2 Score

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting Rx e.g. amiodarone for rhythm control)	1
T	Tobacco use (within two years)	2
R	Race (non-Caucasian)	2

Score result

0-2	Patients are likely to achieve a high TTR (e.g. >65%) so initiating with a VKA is likely beneficial.
≥2	Improve education regarding anticoagulation control (e.g. a structured educational programme) or select a NOAC would be better initial options.


P=0.016*
43
41
39
37
35
33
TTR (%)
41.0
39.0
36.0
2
n=254
3
n=646
4-6
n=528
SAMe-TT2R2 score

Advantages and disadvantages of vitamin K antagonists and novel oral anticoagulants

	Vitamin K antagonists	Novel oral anticoagulants
Pharmacological properties	Multiple coagulation factors target	Single coagulation factor target
	Slow onset of action	Fast onset of action
	Long half-life	*Short half-life*
	Almost entirely hepatic metabolism	*Variable percentage of renal clearance*
	Narrow therapeutic window	Wide therapeutic window
	Wide inter- and intraindividual variability in dose–response	Low inter- and intraindividual variability in dose–response
	Food interactions	Low potential for food interactions
	Many drug interactions	*Some drug interactions*
Indications and contraindications	Broad spectrum of indications	Licensed for VTE prevention in orthopedic surgery, VTE treatment, ACS, stroke prevention in non-valvular AF
	Applicable in patients with MHV or valvular AF	Not applicable in patients with MHV or valvular AF
Bleeding complications and other side effects	Higher risk of intracranial bleeding	Lower risk of intracranial bleeding
	Lower risk of gastrointestinal bleeding	Higher risk of gastrointestinal bleeding
	Rarely other side effects (skin necrosis and purple toe syndrome)	Dyspepsia (dabigatran)
	Protective effect on ACS	Potential increased risk of ACS (dabigatran)

- The half-lives of the NOACs can be significantly prolonged in patients with renal impairment and doses may accumulate; patients can deteriorate very quickly in the event of an acute decline in renal function due to an acute co-morbidity (e.g. dehydration, shock, or the initiation of nephrotoxic medicines such as NSAIDs, ACE inhibitors, or aminoglycosides).

eGFR >50 for dabigatran;

eGFR >30 for rivaroxaban;

eGFR >30 for apixaban.

- Dabigatran is contraindicated in patients with creatinine clearance <30mL/min; in patients with creatinine clearance 30-50mL/min the dose of dabigatran (150mg twice daily or 110mg twice daily) should be selected based on an individual assessment of both thromboembolic and bleeding risk.
- Rivaroxaban is not recommended if creatinine clearance <15mL/min. It should be used with caution in patients with creatinine clearance 15-29mL/min and a low dose of 15mg once daily is recommended.
- Apixaban is not recommended if creatinine clearance <15mL/min. A low dose of 2.5mg twice daily is recommended in patients with creatinine clearance 15-29mL/min, or with a serum creatinine ≥1.5mg/dl associated with age ≥80 years or bodyweight ≤60kg,

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NOACs and GI Bleed

- NOACs have higher risk of GI Bleed compared with warfarin.
- Risk factors of NOAC-related GI Bleed include concomitant use of ulcerogenic agents, older age, renal impairment, *Helicobacter pylori* infection and a past history of GI Bleed.
- NOACs may inhibit GI mucosal healing. In addition, the tartaric acid in dabigatran etexilate is postulated to cause direct injury.
- On the other hand, the bioavailability of warfarin is more than 95%, and non-absorbed warfarin does not have any topical effect
- Prevention of NOAC-related GIB includes proper patient selection, using a lower dose of certain NOACs

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Warfarin is protective in ACS

- Trials e.g. WARIS –II, ASPECT-2 and a Meta-analysis of 10 trials including 5938 patients.
- Warfarin in combination with aspirin was associated with a significantly lower risk of myocardial infarction (risk ratio, RR, 0.56), and revascularization (RR 0.80)
- Lowest risk/benefit ratio was observed in patients at high ischaemic risk and low bleeding risk.

Dabigatran increases Myocardial Infarction

- RE-LY trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin.
- A Meta-analysis of seven trials including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis-

  Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group including warfarin, enoxaparin, or placebo administration.
- Risks were not heterogeneous for all analyses (I(2) = 0%; P ≥ .30) and were consistent using different methods and measures of association.

Arch Intern Med. 2012;172(5):397-402

Contd..

Laboratory tests	Need for regular anticoagulation monitoring	Fixed dose regimen without the need for monitoring drug levels and therapeutic effect
	Monitoring through INR	No standardized monitoring test
Reversal of the anticoagulant effect	Availability of antidote (vitamin K1)	*Specific antidotes under development*
	Established reversal strategy	Limited experience regarding the re-versal strategy
Peri-procedural management	Longer preoperative interruption (5 d before)	Shorter pre-operative interruption (generally 1–2 d before)
	Need for heparin bridging therapy	No routine need for heparin bridging therapy
Patients' education and adherence	Lifestyle changes required	*Less lifestyle changes required*
	Inconvenience of routine monitoring (white-coat adherence)	*Routine monitoring not required (potential lower adherence)*
	Once-daily administration	*Once or twice-daily administration*

Patients receiving anticoagulation should be kept under ongoing surveillance.

- Track compliance
- Record relevant blood results
- Calculate creatinine clearance
- Monitor adverse events
- Record dosing information
- Record risk assessment CHA_2DS_2 VASc and HAS-BLED score

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INRange system

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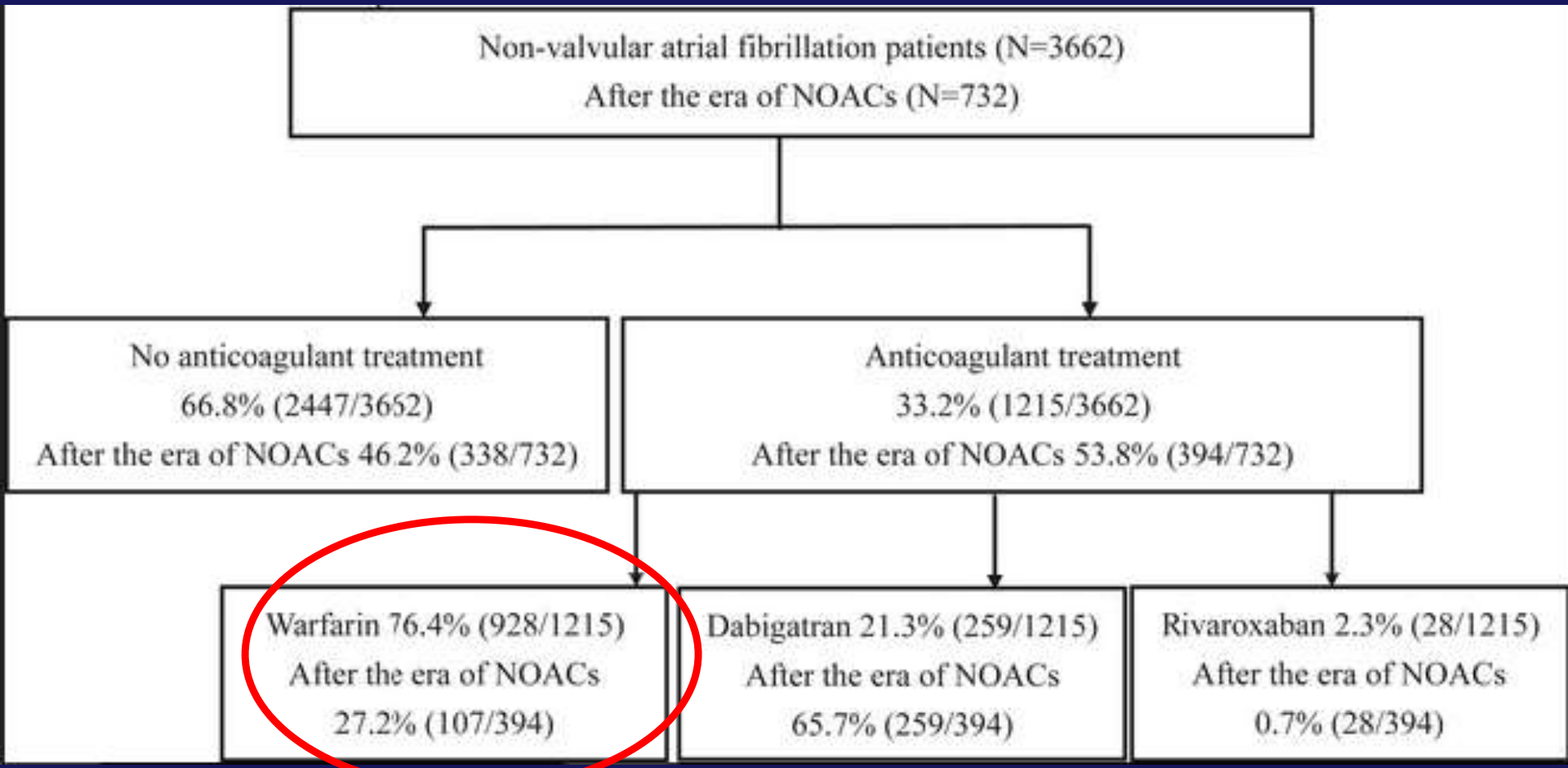
NOACs induced bleeding

- These drugs are not routinely monitored, which leads to an increased risk of unwanted elevation of serum levels and the associated risk of hemorrhage.
- With the exception of dabigatran, no NOAC has a specific antidote.
- Dabigatran has a direct inhibitor, idarucizumab (Praxbind), which is relatively safe, works within about 45 minutes and provides full reversal for up to 24 hours in most patients but is very expensive — about **$3,500 per dose**.
- Vitamin K and plasma, standard antidotes for warfarin, aren't effective for NOACs.
- Plasma can be tried in an emergency situation, but there is risk and no clear benefit.
- Clearance of the drug from system takes 24 to 72 hours, depending on a patient's liver and kidney function.

National Taiwan University Hospital's electronic database to identify all nonvalvular AF patients from January 1, 2007 to December 31, 2013.



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SUMMARY

- Warfarin in properly selected patients maintaining a good TTR is a reasonable option even in non-valvular AF.
- NOACs should be better avoided in advanced Kidney disease and GI Bleed.
- Warfarin has a protective role in ACS while dabigatran has an increased risk of MI.
- NOACs lack easily available antidotes and hence bleeding induced by them are often difficult to manage.

Thank you